

What is claimed is:

1. An isolated, modified IMPDH polypeptide comprising an oligo-peptide domain substituted for a subdomain of a wild-type IMPDH polypeptide, the substitution
5 resulting in a modified IMPDH polypeptide, which is shorter in length compared to the wild-type IMPDH polypeptide.
2. The modified IMPDH polypeptide of claim 1, wherein the wild type IMPDH polypeptide is type I or type II IMPDH.
- 10 3. The modified IMPDH polypeptide of claim 1, further comprising a first IMPDH catalytic core domain and a second IMPDH catalytic core domain.
4. The isolated, modified IMPDH polypeptide of claim 3, wherein the oligo-peptide
15 domain is located between the first and the second IMPDH catalytic core domains.
5. The isolated, modified IMPDH polypeptide of claim 3, wherein the first IMPDH catalytic core domain is located N-terminal to the second IMPDH catalytic core domain.
- 20 6. The modified IMPDH polypeptide of claim 1, wherein the oligo-peptide domain comprises a tri-peptide.
7. The modified IMPDH polypeptide of claim 1, wherein the oligo-peptide domain
25 comprises a tetra-peptide.
8. The modified IMPDH polypeptide of claim 1 having the amino acid sequence as shown in any one of SEQ ID NOS.: 20-39.
- 30 9. The modified IMPDH polypeptide of claim 6, wherein the tri-peptide has an amino acid sequence as shown in any one of SEQ ID NOS.:1-10.

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10. The modified IMPDH polypeptide of claim 7, wherein the tetra-peptide has an amino acid sequence as shown in any one of SEQ ID NOS.:11-19.
- 5 11. The isolated, modified IMPDH polypeptide of claim 6, wherein the first amino acid position of the tri-peptide sequence is selected from the group consisting of aspartic acid, threonine, serine, or glycine, lysine, isoleucine and alanine.
12. The isolated modified IMPDH polypeptide of claim 6, wherein the second amino acid
10 position of the tri-peptide sequence is selected from the group consisting of lysine, proline, alanine, valine, leucine, glycine and serine.
13. The isolated modified IMPDH polypeptide of claim 6, wherein the third amino acid
15 position of the tri-peptide sequence is selected from the group consisting of tyrosine, serine, threonine, glycine, phenylalanine, isoleucine, histidine, and aspartic acid.
14. The isolated modified IMPDH polypeptide of claim 7, wherein the first amino acid
20 position of the substitute tetra-peptide sequence is selected from the group consisting of glycine, glutamine, asparagine, serine, threonine, tyrosine, and alanine.
15. The isolated modified IMPDH polypeptide of claim 7, wherein the second amino acid
position of the substitute tetra-peptide sequence is selected from the group consisting of serine, glycine, proline, isoleucine, and arginine.
- 25 16. The isolated modified IMPDH polypeptide of claim 7, wherein the third amino acid position of the substitute tetra-peptide sequence is selected from the group consisting of serine, glutamine, threonine, tyrosine, isoleucine, proline, and arginine.
17. The isolated modified IMPDH polypeptide of claim 7, wherein the fourth amino acid
30 position of the substitute tetra-peptide sequence is selected from the group consisting of tryptophan, proline, leucine, serine, glutamine, threonine, and tyrosine.

18. A protein multimer, comprising between 1 and 8 modified IMPDH polypeptides in association with each other, wherein the modified IMPDH polypeptides each comprise an oligo-peptide domain substituted for a subdomain of a wild-type IMPDH polypeptide resulting in the modified IMPDH polypeptide, which is shorter in length compared to the wild-type IMPDH polypeptide.
19. The protein multimer of claim 18 which is a dimer.
20. The protein multimer of claim 18 which is a tetramer.
21. The protein multimer of claim 18 which is an octamer.
22. A nucleic acid molecule comprising a polynucleotide sequence which encodes any one of the modified IMPDH polypeptides of claim 8.
23. The nucleic acid molecule of claim 22 which is RNA.
24. The nucleic acid molecule of claim 22 which is DNA.
25. A nucleic acid molecule comprising a polynucleotide sequence which is complementary to the polynucleotide sequence of claim 24.
26. The nucleic acid molecule of claim 22, 23, 24 or 25 which is labeled with a detectable marker.
27. The nucleic acid molecule of claim 26, wherein the detectable marker is selected from the group consisting of a radioisotope, a fluorescent compound, a bioluminescent compound, a chemiluminescent compound, a metal chelator, and an enzyme.

28. A vector comprising a polynucleotide sequence which encodes any one of the modified IMPDH polypeptides of claim 8.

29. A host-vector system comprising the vector of claim 28 in a suitable host cell.

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30. The host-vector system of claim 29, wherein the suitable host cell is from an organism which is selected from the group consisting of bacteria, yeast, mammals, insects, and plants.

10 31. A method for producing a modified IMPDH polypeptide comprising:

- a) culturing the host-vector system of claim 30 under suitable conditions so as to produce the modified IMPDH polypeptide; and
- b) recovering the modified IMPDH polypeptide so produced.

15 32. The modified IMPDH polypeptide produced by the method of claim 31.

33. A monoclonal antibody reactive with the modified IMPDH polypeptide of claim 1 or 32.

20 34. The monoclonal antibody of claim 33 which is labeled with a detectable marker.

35. The monoclonal antibody of claim 34, wherein the detectable marker is selected from the group consisting of a radioisotope, a fluorescent compound, a bioluminescent compound, a chemiluminescent compound, a metal chelator, and an enzyme.

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FOOTNOTES

36. A method for identifying an agent of interest that inhibits the activity of a protein multimer comprising modified IMPDH polypeptides, the method comprising:

- 5 a) contacting the protein multimer with inosine-5'-monophosphate, nicotinamide adenine dinucleotide, and the agent of interest; and
- b) detecting the level of the reduced form of inosine-5'-monophosphate or nicotinamide adenine dinucleotide which is generated, whereby a low level of the reduced form of inosine-5'-monophosphate or nicotinamide adenine dinucleotide generated indicates that the agent of interest inhibits IMPDH
- 10 activity.

37. The method according to claim 36 which comprises contacting a plurality of substantially identical samples each separately with a different agent of interest.

15 38. The method of claim 37, wherein the plurality of samples comprises more than about 10^4 samples.

39. The method of claim 37, wherein the plurality of samples comprises more than about 10^5 samples.

20 40. The method of claim 37, wherein the plurality of samples comprises more than about 10^6 samples.

25 41. The method of claim 40, wherein the plurality of substantially identical samples are each contacted essentially simultaneously with a different agent of interest.

42. A method for improving resolution of an X-ray crystal structure of an IMPDH polypeptide or IMPDH polypeptide complex comprising removing a subdomain of the IMPDH polypeptide thereby improving the resolution of the X-ray crystal

30 structure of the IMPDH polypeptide or IMPDH polypeptide.

52. The method of claim 51, wherein the tetra-peptide has an amino acid sequence as shown in SEQ ID NOs:11-19.

5 53. A modified IMPDH polypeptide comprising an amino acid sequence as shown in any one of SEQ ID NOS.:20-39.

54. An isolated nucleic acid molecule comprising the nucleic acid sequence as shown in any one of SEQ ID NOS.:40-47.

10 55. A modified IMPDH polypeptide, wherein amino acids 111-243 as shown in any one of SEQ ID NOS:48, 49, 62, 63, 64, or 65 are replaced with a tripeptide.

15 56. A modified IMPDH polypeptide, wherein amino acids 111-243 as shown in any one of SEQ ID NOS:48, 49, 62, 63, 64, or 65 are replaced with a tetrapeptide.